

The Importance of Insulin Resistance in the Pathogenesis of Type 2 Diabetes Mellitus

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Many patients with type 2 diabetes have hyperglycemia as a result of deficiencies in both insulin secretion and insulin action, that is, β -cell dysfunction and insulin resistance. Insulin resistance is a state of reduced insulin sensitivity, an inability of insulin to lower plasma glucose levels through suppression of hepatic glucose production and stimulation of glucose utilization in skeletal muscle and adipose tissue. Insulin resistance stems from genetic and environmental causes, and its extent varies considerably among individuals. Studies have shown that enhanced insulin secretion can compensate for insulin resistance and that enhanced insulin sensitivity can mask defects in β -cell function. However, insulin resistance is essential to the development of the majority of cases of type 2 diabetes. Numerous epidemiologic studies have demonstrated an increase in the prevalence of insulin resistance and type 2 diabetes in various ethnic populations that have migrated from their native lands to more urbanized and westernized regions of the world. Type 2 diabetes has already reached epidemic proportions worldwide. By 2025, an estimated 300 million people will have diabetes, most of whom will inhabit China, India, and the United States. These studies have also demonstrated the complex interrelationship of hyperinsulinemia, obesity (primarily visceral adiposity), and free fatty acids with β -cell dysfunction, insulin resistance, and the development of type 2 diabetes. Although little can be done to avert a genetic predisposition to type 2 diabetes, normoglycemia can be preserved in individuals who remain insulin sensitive. Lifestyle changes can be implemented and medications can be administered to improve insulin sensitivity, insulin secretion, and glucose utilization and reduce the prevalence of type 2 diabetes. *Am J Med.* 2000;108(6A):9S-14S. © 2000 by Excerpta Medica, Inc.

Type 2 diabetes is the most prevalent form of diabetes. The pathogenesis of hyperglycemia is rooted in a malfunction of the interrelationship between insulin secretion and insulin action.^{1,2} The islet β -cells of the pancreas act as glucose sensors to maintain a balance between hepatic glucose production and the rate of insulin-dependent utilization of glucose by muscle and adipose tissue. Plasma glucose changes resulting from changes in glucose production and glucose utilization are sensed by the islet β -cells, resulting in adjustments of insulin secretion to achieve a new steady state that restores normal blood glucose levels.

When islet β -cell function is impaired, insulin secretion is inadequate, leading to overproduction of glucose by the liver and underutilization of glucose in peripheral tissues.² The resulting hyperglycemia increases insulin secretion by the β -cells. Relatively less β -cell dysfunction is necessary for hyperglycemia to occur in the presence of insulin resistance. Thus, hyperglycemia may result from a deficiency in either insulin production and secretion or insulin action. In most cases, both insulin secretion and insulin action are deficient.

PATHOPHYSIOLOGIC ABNORMALITIES IN TYPE 2 DIABETES

The pathophysiologic abnormalities of type 2 diabetes range from a metabolic state of predominant insulin resistance with relative β -cell dysfunction to a state of severe β -cell dysfunction accompanied by some insulin resistance. Insulin resistance is essentially a condition of reduced insulin sensitivity. Insulin sensitivity is commonly described as the ability of insulin to lower plasma glucose levels, which it does by suppressing hepatic glucose production and stimulating glucose utilization in skeletal muscle and adipose tissue.

Both inherited and acquired influences contribute to the development of insulin resistance. The inherited defects responsible for the more common forms of insulin resistance, which are typically seen in individuals with type 2 diabetes, are largely unidentified. Although mutations in insulin receptors, glucose transporters, and signaling proteins have been identified, these are relatively rare. The acquired causes of insulin resistance include inactivity, overeating, aging, hyperglycemia, increased levels of free fatty acids (FFAs), and the effects of some medications.

Studies of the relationship between the insulin secre-

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tory capacity of β -cells and insulin sensitivity in nondiabetic persons support the view that insulin secretion can compensate for insulin resistance, or that enhanced insulin sensitivity can mask an insulin secretory defect.² Furthermore, insulin sensitivity varies widely among individuals with normal glucose tolerance; it is highest among white males and females and prepubertal children. Insulin resistance is found at puberty, in the elderly, with obesity, during pregnancy, and among many nonwhite populations.²

WORLDWIDE PREVALENCE OF DIABETES

Epidemiologic data indicate that insulin resistance is essential to the development of type 2 diabetes in most patients. Worldwide prevalence data indicate that diabetes has reached epidemic proportions.³ The vast majority of cases of diabetes are type 2. A particularly interesting finding is that the prevalence increases as ethnic groups migrate from lesser-developed areas of the world to more urban or westernized regions.⁴ For example, the prevalence of diabetes among the Chinese living on the island of Mauritius is much higher than that among the Chinese living in mainland China (**Table 1**). Notable differences are also found for Asian Indians, Micronesians, and Polynesians.

Recent prevalence estimates compiled by the World Health Organization (WHO) give credence to the belief that the prevalence of diabetes is increasing at a rapid rate and that the international burden of diabetes appears to be shifting.⁵ In 1995, an estimated 135 million people had diabetes, and more than half were from only three countries—India, China, and the United States. By 2025, the number of people with diabetes is expected to rise to about 300 million; again, most of these individuals will be from the same three countries. In developed countries, the number of people with diabetes will increase by 42%, from 51 million to 72 million, while the increase in lesser-developed countries is expected to be 170%, from 84 million to 228 million. These increases in prevalence will not result solely from population increases but from an increased prevalence of insulin resistance.

In the United States, the prevalence of diabetes is higher in virtually every ethnic minority group than in the white population (**Figure 1**).^{6–11} Given the pattern of growth in the African American, Latino, and Asian American populations in the United States, an increasing proportion of the diabetes burden in this country is expected to be borne by these ethnic groups in the new millennium.

LESSONS LEARNED FROM MIGRANT POPULATIONS

A greater understanding of the pathophysiology of type 2 diabetes has come from studies of migrant populations.

Table 1. Examples of Worldwide Age-Adjusted Prevalence of Diabetes

Population	Prevalence (%)
Melanesian (New Guinea)	0
Bantu	1.2
Chinese (China)	1.6
Asian Indian (rural India)	2.7
Polynesian (rural West Samoa)	4.0
Micronesian (rural Kiribati)	4.3
White (United States)	6.1
Melanesian (urban Fiji)	8.6
Black (United States)	10.3
Polynesian (urban West Samoa)	10.5
Chinese (Mauritius)	13.1
Mexican American	14.1
Asian Indian (Fiji)	22.0
Micronesian (Nauru)	41.3
Native American (Pima)	50.3

Adapted from *National Diabetes Data Group: Diabetes in America*.⁶

For example, the prevalence of diabetes in Japanese Americans in Seattle was about four times that of the Japanese in Tokyo (**Figure 2**).^{9,10} Despite very similar degrees of hyperglycemia, the Japanese American men with type 2 diabetes in this survey had significantly higher levels of plasma insulin ($P \leq 0.03$) at all time periods during a 75-g oral glucose tolerance test (OGTT) than Japanese men with diabetes (**Figure 3**).^{9,12} This observation strongly suggests a greater degree of insulin resistance among the Japanese American men than among Japanese men. It is possible, then, that the superimposition of insulin resistance in a Japanese population results in the emergence of cases of type 2 diabetes that otherwise would have remained undetected.

In the same study population, the Japanese Americans also had significantly greater body mass index (BMI) than their Japanese counterparts (25.1 vs 21.8; $P < 0.001$).¹² There was a highly significant correlation between BMI value and plasma insulin level ($P \leq 0.01$) at each time-point for the Japanese American men but not for the Japanese men. Even when the plasma insulin data were adjusted for BMI, the difference in fasting insulin levels was still significantly greater for the Japanese American men than for the Japanese men ($P < 0.005$). The results of this study indicate that one or more factors other than BMI were responsible for the differences in plasma insulin levels between the two subgroups.

CORRELATION BETWEEN THE PREVALENCE OF TYPE 2 DIABETES AND OBESITY

Obesity is closely associated with insulin resistance and the development of type 2 diabetes, and an increased prevalence of type 2 diabetes correlates not only with an

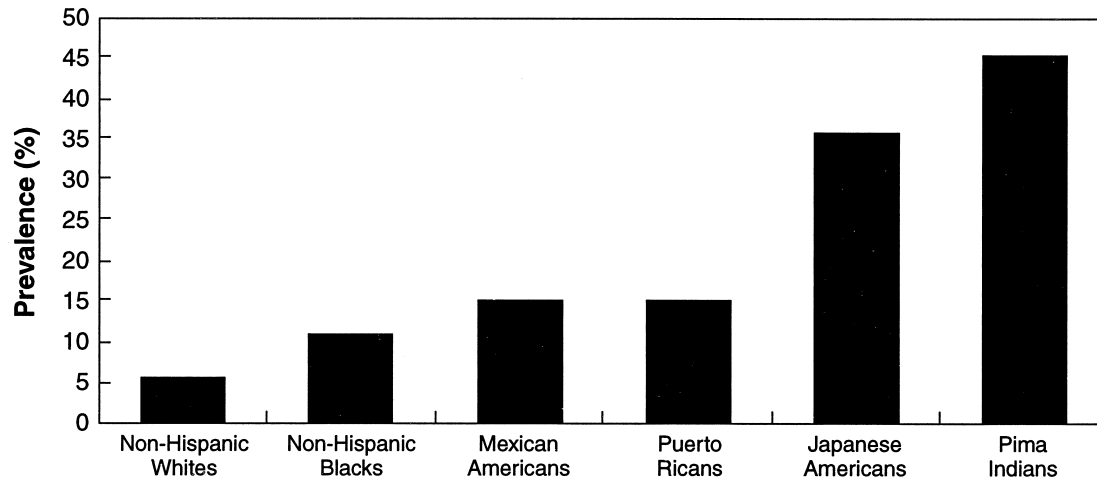


Figure 1. Prevalence of diabetes in the United States by ethnic group, ages 45 to 74 years.⁶⁻¹¹

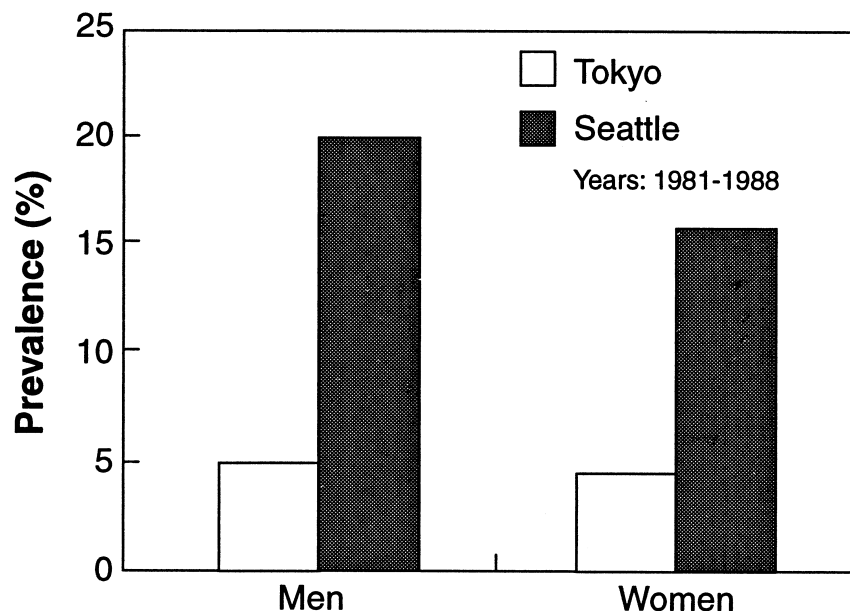


Figure 2. Prevalence of type 2 diabetes in Tokyo (open bars) and Seattle (solid bars) among men and women >40 years of age (1981 to 1988).

increase in the percentage of desirable body weight but with ethnicity or race. For example, the prevalence of diabetes associated with an increase in desirable body weight from 100% to $\geq 140\%$ is higher among Mexican Americans than African Americans and European Americans in the United States, and the prevalence is higher among African Americans than European Americans.

A clearly important factor is the central pattern of body fat distribution (central or visceral adiposity), even in the absence of clinical obesity.^{13,14} In fact, central adiposity is an important clinical clue to the presence of insulin resistance and hyperinsulinemia. Other clinical predictors of insulin resistance and hyperinsulinemia are hypertriglyc-

eridemia and low levels of high-density lipoprotein cholesterol, glucose intolerance, hypertension, atherosclerosis, polycystic ovary syndrome, and ethnicity.

Obesity due to increased visceral adiposity was found to be an especially strong predictor of type 2 diabetes during follow-up of 137 initially nondiabetic Japanese American men.^{14,15} After 2.5 years of follow-up, 13 men had diabetes; by 5 years, 10 more had type 2 diabetes. During an OGTT, the men who had diabetes had reduced incremental insulin secretion at baseline and during follow-up compared with men who remained nondiabetic (Figure 4).¹⁵ In addition, the men who had diabetes had either increased amounts of

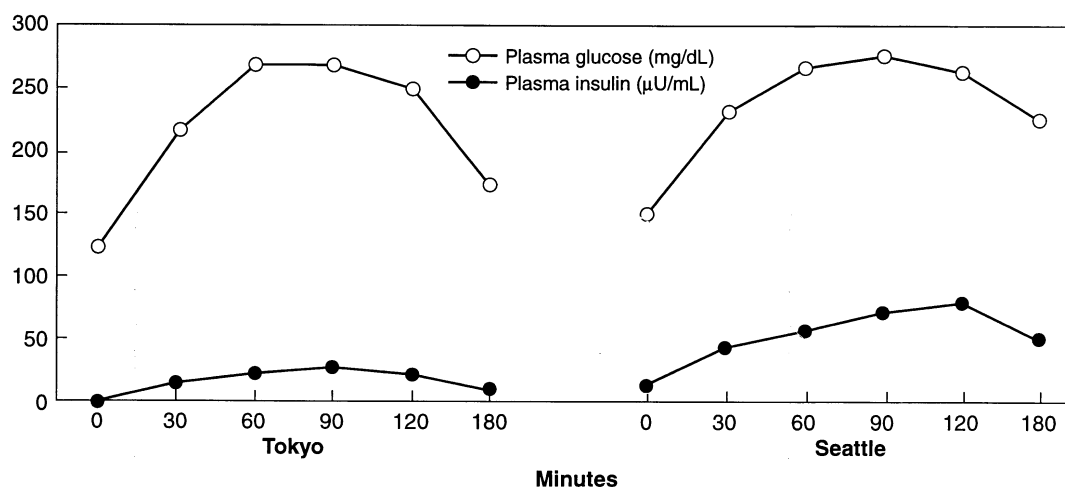


Figure 3. Plasma glucose and insulin levels in Japanese (Tokyo) and Japanese American (Seattle) men with type 2 diabetes during a 75-g oral glucose tolerance test. Open circles = plasma glucose (mg/dL); solid circles = plasma insulin (μ U/mL).⁹

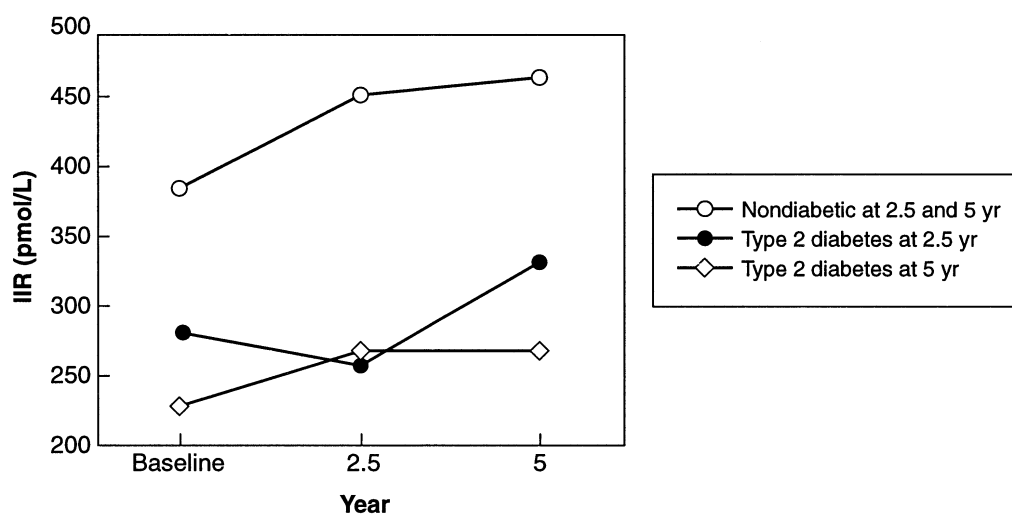


Figure 4. Incremental insulin release (IIR) at baseline and at follow-up in initially nondiabetic Japanese American men by follow-up glucose tolerance status. Open circles = nondiabetic at 2.5 and 5 years; solid circles = type 2 diabetes at 2.5 years; open diamonds = type 2 diabetes at 5 years.¹⁵

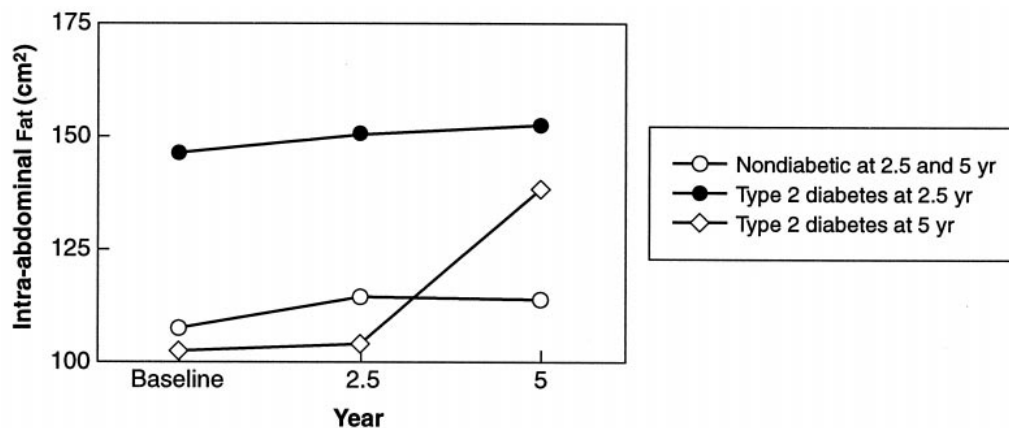


Figure 5. Intra-abdominal fat distribution at baseline and at follow-up in initially nondiabetic Japanese American men by follow-up glucose tolerance status. Open circles = nondiabetic at 2.5 and 5 years; solid circles = type 2 diabetes at 2.5 years; open diamonds = type 2 diabetes at 5 years.¹⁵

visceral fat at baseline or showed an increase in the amount of visceral fat during follow-up (**Figure 5**). BMI, on the other hand, was not a predictor of diabetes in this study population.

These findings strongly suggest that β -cell dysfunction is present in all individuals who eventually have type 2 diabetes. Furthermore, these findings suggest that insulin resistance, known to be associated with central adiposity, is essential to most cases of type 2 diabetes. Some individuals in this study in whom diabetes developed later had an increase in visceral adiposity at baseline, whereas in others the increase in visceral adiposity accompanied the development of diabetes. In the latter group, diabetes appeared to develop after the β -cell could no longer accommodate the additional secretory demand on insulin secretion imposed by visceral adiposity (and accompanying insulin resistance).

FREE FATTY ACIDS AS THE LINK BETWEEN OBESITY AND INSULIN RESISTANCE

FFAs released from adipose tissue have been proposed as a link between obesity and insulin resistance.¹⁶ In this regard, visceral fat is important because it is metabolically more active than subcutaneous fat; therefore, it releases more FFAs. Furthermore, in individuals with visceral adiposity, the FFAs have direct access to the liver, resulting in increased hepatic glucose production and fasting hyperglycemia. In addition, elevated levels of FFAs in the peripheral circulation impair insulin action in peripheral tissues, resulting in increased insulin resistance.

If FFAs are infused into normal individuals, insulin resistance can develop in the form of reduced glucose utilization. FFAs can also blunt the ability of insulin to suppress hepatic glucose production. These results suggest a mechanism whereby obesity—and particularly visceral obesity—may relate to insulin resistance in both peripheral tissues and in the liver.

PANCREATIC β -CELL RESPONSE TO INSULIN RESISTANCE

There is little doubt that a defect in the secretory function of β -cells is present in many patients with type 2 diabetes and that the defect is influenced by genetics and environment. Individuals with abnormal β -cell function can maintain normoglycemia if they remain insulin sensitive. Should they become insulin resistant, however, hyperglycemia and insulin deficiency will develop. Furthermore, hyperglycemia itself contributes to insulin resistance through a mechanism termed glucotoxicity.¹⁷ During euglycemic clamp studies, glucose disposal rates in individuals with type 2 diabetes are markedly reduced compared with individuals who have normal glucose metabolism. When glycemic control in individuals with type 2 diabe-

tes is improved, however, their glucose disposal rates improve but do not reach the levels observed in normal individuals. Thus, glucotoxicity affects glucose disposal, thereby contributing to insulin resistance in peripheral tissues.

To reverse this progression to hyperglycemia, methods need to be developed to improve insulin sensitivity, insulin secretion, and glucose utilization. Lifestyle changes, including increased physical activity and reduced caloric intake, particularly of calories derived from saturated fat, contribute to weight loss and glucose utilization. In addition, medications are available that can reduce hepatic glucose output or increase insulin sensitivity in skeletal muscle and adipose tissue. With implementation of these measures and monitoring of patients at increased risk for type 2 diabetes, we should be able to substantially reduce the prevalence of this disease.

SUMMARY

Studies of the complex relationship between insulin secretion and insulin action indicate that normoglycemia can be preserved in individuals who retain insulin sensitivity, even in the presence of β -cell dysfunction and secretory defects. As ethnic populations migrate to urbanized and westernized regions, individual body weights typically increase, insulin sensitivity is reduced, and the presence of β -cell dysfunction becomes apparent. This result is particularly likely if the pattern of body weight gain is of a visceral or central pattern. Several nonpharmacologic and pharmacologic measures can be taken to prevent or minimize insulin resistance and thereby reduce the prevalence of type 2 diabetes.

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